REMARKS

Claim 39 has been amended. Claim 54 and 55 have been added.

Claims 39-55 are now active in this application.

REQUEST FOR RECONSIDERATION

Applicants wish to thank Examiner Thurman Page for the recent helpful and courteous discussion conducted with their representative, Mr. William Beaumont, and one of the inventors, Arthur Deboeck. During the discussion, Applicants proposed submitting additional experimental data establishing the unexpected superiority arising from the use of roller-dried anhydrous β-lactose versus spray-dried ∝-lactose monohydrate in a particle size range of greater than 160μm in order to fairly establish the unexpected superiority for the entire claimed particle size range of between 50 and 250 μm for roller-dried anhydrous β-lactose excipient.

The present invention provides a dry powder inhaler composition containing:

1. One or more particular active ingredients, and
2. A roller dried anhydrous β-lactose having a mean particle size comprised between 50 and 250 μm, and a rugosity comprised between 1.9 and 2.4.

The various aspects of terms within independent Claim 39 are discussed below.

a) *Dry powder inhaler* (DPI) is a system designed for the inhalation and/or lung administration of dry powders. DPI's by definition do not contain liquids under any form (solvent, propellant, liquified gazes...). This is axiomatic by definition.

b) *One or more particulate active ingredients* are also called drugs. The drug or drugs are present in the solid (particulate) form. The drug is not in solution and/or in suspension. See a) above. The particle size for lung administration is generally comprised between about 0.5 and 10 μm.

c) *Roller-dried anhydrous β-lactose.* The β-anhydrous lactose is produced from a solution of lactose in water (in water the lactose is in the β-form) which is dried extremely rapidly (water is evaporated) using counter-clock rotating steam heated drums for instantaneous water removal. This fast removal is essential to avoid the transformation of the β-lactose into ∝-lactose. Also, the roller-dried β-lactose of the present invention has a rugosity comprised between 1.9 and 2.4.

d) *β-lactose carrier particle size of between 50 and 250μm.*

The consequence of the use of β-lactose with a particle size comprised between 50 and 250μm have been investigated with considerable detail, and the results thereof are described in the present specification of page 12, table 2 and are summarized further below. See also page 8 of the present specification.

Before proceeding, however, it is noted, in particular that the preamble term "dry powder inhaler pharmaceutical composition" is a claim limitation that must be given weight in the interpretation of all of claims 39-53. Under the standard of Lactate Corp. v. Ultraseal, Ltd., 228 U.S.P.Q. 90 (Fed. Cir. 1985), this preamble term "breathes life and meaning into the claims."

At the onset, attention is directed to page 12 of the present specification which evidences the unexpectedly superior pulmonary fraction (%) obtained when using roller-dried β-lactose as compared to spray-dried ∝-lactose in the claimed particle size ranges.

Specifically, the following table shows the influence of the nature and particle size of lactose carrier on the in vitro pulmonary fraction, expressed as percent of total dose, of NAL (active ingredient) measured by using the twin impinger at 60 L/min.

NOTE: The higher the values the better the carrier.

	∝-lactose			β-lactose		
Particle Size [μm]	**63 - 100**	**96 - 125**	**100 - 160**	**63 - 100**	**96-125**	**100 - 160**
Pulmonary Fraction [%]	28	28	28	35	39	42

The pulmonary fractions are 28% for ∝-lactose (spray-dried ∝-lactose monohydrate) versus 35 to 42% for β-lactose (roller-dried anhydrous β-lactose) with an increase of 25 % to 50 % for the latter over the former.

This clearly demonstrates, the unexpected superiority arising from the use of roller-dried anhydrous β-lactose versus spray-dried ∝-lactose monohydrate as a carrier for the claimed particle size range for DPI inhalation compositions. Clearly, one skilled in the art would have no reason to expect this result in view of the art of record.

During the discussion with Examiner Page, Applicants' representative asserted that the above experimental data were clear support for both: 1) the unexpected superiority of the entire claimed particle size range of roller-dried anhydrous β-lactose excipient of from between 50 to 250 μm, and thus 2) the patentability of the present invention.

In view of the remarks set forth in that discussion, and to buttress the same, Applicants have now further conducted an additional experiment to demonstrate the unexpected superiority of the particle size range of 150 to 250 μm for roller-dried anhydrous β-lactose excipient as compared to spray-dried ∝-lactose monohydrate excipient of the same particle size range. These experimental results are shown in the attached Declaration under 37 C.F.R. §1.132.

Specifically, an experiment was conducted comparing the effect on available pulmonary fraction of active ingredient using roller-dried anhydrous β-lactose excipient as compared to spray-dried ∝-lactose monohydrate in the particle size range between 150 to 250μm for two

different active ingredients, i.e., NAL and Budenoside. The pulmonary fraction was measured using the multistage liquid Impinger at 100 l/min. during a period of 2.4 seconds.

		FPD in percent (%)		
Active Drug	**Ratio Active/Lactose w/w**	**Anhydrous roller dried β lactose 150-250 μm**	**Spray dried α lactose monohydrate 150-250μm**	**Difference in Percent [%]**
NAL	1/4	28	25	12
Budesonide	1/100	31	24	29

The in-vitro fine particle dose (FPD) obtained with the formulation continuing the roller-dried anhydrous β-lactose having a particle size of between 150 to 250 μm is significantly greater (12% and 29% for NAL Budenoside respectively) than that obtained with formulations containing the same active ingredient and spray-dried ∝-lactose monohydrate excipient in the same particle size range of between 150 to 250 μm.

Clearly, these results demonstrate the unexpectedly superior pulmonary fractions afforded by the use of roller-dried anhydrous β-lactose excipient as compared to spray-dried ∝-lactose monohydrate excipient for the particle size range of 150 to 250 μm. Thus, in conjunction with the unexpectedly superior results demonstrated for the use of the particle size range of 63 to 150 μm in the present specification for the roller-dried anhydrous β-lactose excipient, the complete evidence of record now clearly evidences beyond reproach the unexpected superiority arising from the use of roller dried anhydrous β-lactose excipient for the entire claimed particle size range of between 50 to 250μm.

Claims 38-53[1] stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sarlikiotis et al. '287 in view of the combination of Stevenson et al. '578 and Cutie et al. '419.

[1] Page 2 of the Official Action of October 7, 2005 recites that claims 38-53 stand so rejected. For purposes of this Amendment, it is assumed that the Examiner intended the rejection of claims 38-53.

However, none of these references either alone or in combination discloses or suggests the present invention.

Notably, Sarlikiotis et al. merely disclose compositions for inhalation containing a micronized active ingredient with a mean particle size of 0.1μm to 10μm and a pharamaceutically acceptable excipient having a mean particle size of 200 to 1,600μm and a rugosity greater than 1.75. Further, this reference discloses the use of any physiologically-acceptable excipient such as inorganic salts, organic salts, monosaccharicdes, disaccharides, polysaccharides, oligosaccharides or mixtures thereof. In particular, as to the dissacharides, this reference merely describes the use of "commercially available lactose" without further elaboration. Clearly, this reference neither discloses nor suggests the use of β-lactose, and certainly not the use of roller-dried anhydrous β-lactose having a particle size of 50 to 250μm.

Stevenson et al. fails to correct the deficiencies of Sarkiliotis et al. as the former merely describes an inhalation formulation containing crystalline lactose of a particle size below 400μm. Moreover, this reference fails to either disclose or suggest the use of roller-dried anhydrous β-lactose having a particle size of 50 to 250μm.

Cutie et al. fails to remedy the deficiencies of both of the above references as this reference merely discloses the use of β-lactose as an excipient in an aerosol drug formulation which consists of a pollution and/or suspension and/or a combination of solution and suspension (slurry) of the drug in a liquid. As noted previously, this type of being drug dispensing system is known as a Metered Dose Inhaler (MDI) system, and not a Dry Powder Inhaler (DPI) system.

Further, Cutie et al. disclose the use of a micronized β-lactose (in the range of a single digit particle size), which is quite different from the roller-dried anhydrous β-lactose of present claims 39-55 having a particle size of 50 to 250μm.

Additionally, Cutie et al. disclose the use of sugars, such as lactose, mannitol, fructose and galactose, and clearly neither discloses nor suggests superior results arising from the use of roller-dried anhydrous β-lactose as compared to spray-dried ∝-lactose monohydrate as clearly demonstrated by the evidence of record in the present application.

In summary, even the combined disclosures of the cited references of record would have failed to disclose or suggest to one skilled in the art at the time the present invention was made that

for DPI formulations, a notably superior pulmonary fraction is available when using roller-dried anhydrous β-lactose as an excipient as compared to using spray-dried ∝-lactose monohydrate as an excipient.

It is well-settled that something in the prior art must suggest the desirability of making the claimed combination. See Uniroyal, Inc. v. Rudkin-Wiley Corp.[2] As noted above, none of the cited references, either alone or in combination, discloses or suggests a dry powder inhaler pharmaceutical composition containing a mixture of one or more particulate pharmaceutically active ingredients and a particulate roller-dried anhydrous β-lactose excipient, said excipient having a particle size comprised between 50 and 250μm, and a rugosity comprised between 1.9 and 2.4.

Further, the rebuttal evidence of unobviousness relied upon, both from the present specification and the attached Rule 132 Declaration, is commensurate in scope with the particle range of between 50 and 250μm for the particulate roller-dried anhydrous β-lactose. See In re Kerkhoven.[3]

Thus, in summary: 1) the Examiner has failed to establish a *prima facie* case of obviousness against the subject matter of all of the present claims, and 2) even assuming, *arguendo*, that he has, Applicants have clearly rebutted any presumption of obviousness.

Hence, this ground of rejection is believed to be unsustainable and should be withdrawn.

Accordingly, it is believed that this application is now in condition for allowance. Early notice to this effect is earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including

[2] 5 U.S.P.Q. 2d 1434 (Fed. Cir. 1988), cert. denied, 488 U.S. 825 (1988).
[3] 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

extension of time fees, to Deposit Account 07-1337 and please credit any excess fees to such deposit account.

Respectfully submitted,

LOWE HAUPTMAN & BERNER, LLP

William E. Beaumont
Registration No. 30,996

Customer Number: 22429
1700 Diagonal Road, Suite 300
Alexandria, Virginia 22314
(703) 684-1111 **WEB/sj**
(703) 518-5499 Facsimile
Date: **January 5, 2006**